

## **REMARKS**

### **A. BACKGROUND**

By this paper, claims 1 and 2 are amended; no claims are canceled or newly added. Accordingly, claims 1, 2, 7, and 14 are currently pending. Applicants respectfully request entry of the amendments herein prior to examination of the application and favorable consideration of the pending claims.

### **B. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH**

The PTO rejected claims 1, 2, 7, and 14 under 35 U.S.C. § 112, first paragraph. In particular, the PTO rejects the claims because the limitation "molecular weight of 10,000 g/ml" is not supported in the specification. (Office Action, pg. 3).

In response, Applicant notes that the claims filed in the Response filed 30 September 2010 include no such limitation. Amended claim 1 filed in the Response of 30 September 2010 included the limitation "molecular weight of 10,000 g/mol." This has been confirmed in PAIR. Applicant respectfully requests withdrawal of this rejection because all of the claims comply with the §112, first paragraph requirement.

### **C. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH**

The PTO rejected claims 1, 2, 7, and 14 under 35 U.S.C. § 112, second paragraph. For at least the reasons listed above with respect to the rejection under 35 U.S.C. § 112, first paragraph, Applicant respectfully submits that the rejection under § 112, second paragraph is moot.

### **D. CLAIM REJECTIONS UNDER 35 U.S.C. § 103**

The Office Action rejected claims 1, 2, 7, and 14 under 35 U.S.C. § 103(a) as being unpatentable over *Schlag* et al. (US 6,358,918) ("*Schlag*") in view of *Hallström* et al. (*Hallström* et al. (2002) *Circulation*, 105, 3032-3038) ("*Hallström*"). Applicant respectfully submits that *Schlag*, either alone or in combination with *Hallström*, fails to teach or suggest each and every element of claim 1 and the claims that depend thereon. Moreover, Applicant respectfully submits that claim 1 and the claims that depend thereon are not obvious in view of *Schlag* and

*Hallström* due to surprising and unexpected results. Reconsideration and allowance of the presently pending claims is respectfully requested.

Claim 1 is directed to a method for the treatment of ischemia. The method of claim 1, as amended, includes administering a pharmaceutical preparation that includes a therapeutic protein having "S-nitroso albumin" and "reduced glutathione." Thus, claim 1 requires both nitrosated albumin and reduced glutathione in the same therapeutic composition.

Applicant respectfully submits that *Schlag*, either alone or in combination with *Hallström*, fails to teach or suggest each and every element of claim 1 because *Schlag* in view of *Hallström* does not teach or suggest a pharmaceutical preparation that includes both S-nitroso albumin and reduced glutathione in the same therapeutic composition.

With respect to *Schlag*, the PTO states that *Schlag* teaches

a method of treating an ischemia (cerebral ischemia) comprising administering ... a pharmaceutical composition comprising at least one (plurality) thiol nitrosated (i.e., S-nitroso) thiol-group containing protein, wherein "at least one" encompasses more than one S-nitroso-proteins that include S-nitroso-albumin (patent claims 21). Said pharmaceutical composition may comprise any proteins including a low-molecular weight proteins with free thiol group, e.g., reduced glutathione (col. 2, lines 51-52 and 61-62).<sup>1</sup>

In col. 2, lines 58-59, *Schlag* says that the proteins may be "nitrosated or capable of being nitrosated," but *Schlag* says nothing about one protein being nitrosated and another reduced. As mentioned, Claim 1 requires administering both "S-nitroso albumin" and "reduced glutathione". The PTO has the burden to show that it would be obvious to select this particular combination.

The Office Action acknowledges that *Schlag* does not "expressly disclose or provide working example for combined use of S-nitroso-albumin (S-NO-HAS) and S-nitroso-glutathione (GSH)<sup>2</sup> for treating the ischemia." (Office Action p. 5, ¶ 1). Indeed, *Schlag* merely teaches a "mixtures of proteins" that are "nitrosated or capable of being nitrosated." (col. 2, lines 58-59).

The Office Action then sets forth an alleged rationale why one of skill in the art would modify *Schlag* in view of *Hallström*. The Office Action states that "reduced glutathione (GSH) has ability of destructing radicals [sic] such as 'O<sub>2</sub>' and GSH serves as the first line of defense

<sup>1</sup> Applicant's note that *Schlag* at col. 2, lines 61-62 uses the term "glutathione" but does not say it is "reduced" as alleged in the Office Action. Applicant respectfully requests that *Schlag* be accurately quoted.

<sup>2</sup> It appears that the Examiner erred in stating "s-nitroso-glutathione". The claim requires "reduced glutathione" and the discussion following the err relates to "reduced glutathione".

against tissue injury (ischemia/reperfusion, see abstract, Hallstrom et al.) due to oxygen toxicity caused by said radical (see p.3037, right col., last paragraph, lines 1-10, Hallstrom et al.)." (Office Action, pg. 5). The Office Action relies on *Hallström* for its explanation of "reduced glutathione" and alleges that one of skill in the art would combine *Schlag* and *Hallström* to yield the claimed invention.

Nevertheless, Applicant respectfully submits that *Hallström* does not teach administering glutathione at all. The description of "reduced glutathione" as set forth in cited section of *Hallström* relates not to administration of reduced glutathione but instead relates to glutathione that naturally exists in a subject. The section of *Hallström* cited in the Office Action merely presents a discussion of the effect on the ratio of reduced glutathione (GSH) to oxidized glutathione (i.e., glutathione disulfide or GSSG) in ischemic subjects. The ratio of reduced glutathione to oxidized glutathione is often used as a measure of oxidative stress. The only thing that *Hallström* shows with respect to glutathione is that ischemic subjects who receive nitrosated albumin alone have a better GSH:GSSG ratio as compared to subjects that are administered native albumin. In no instance does *Hallström* teach or suggest administering reduced glutathione to a subject, either alone or in combination with nitrosated albumin.

Applicant respectfully submits that one of skill in the art viewing *Hallström* would not find it obvious to administer reduced glutathione with nitrosated albumin since *Hallström* teaches that reduced glutathione already exists in the body of the subject and that naturally occurring reduced glutathione provides the benefit described by *Hallström*. Thus, the teachings of *Hallström* suggest that administration of nitrosated albumin is by itself sufficient. In contrast, the Applicant has shown that, surprisingly, despite the presence of naturally occurring reduced glutathione in a subject, there is a significant benefit to administering reduced glutathione with nitrosated albumin.

Examples 1-3 of the present Application (See Application ¶¶ [0062]-[0076]) describe several different types of synergistic effects that were observed when S-nitroso albumin was administered in combination with reduced glutathione as compared to the administration of S-nitroso albumin alone. Example 1 demonstrates a drop in blood pressure when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone; Example 2 demonstrates an increase in NO release when S-nitroso albumin was administered in combination with reduced glutathione as compared to

administering S-nitroso albumin alone; and Example 3 demonstrates a drop in platelet aggregation when S-nitroso albumin was administered in combination with reduced glutathione as compared to administering S-nitroso albumin alone. Examples 1-3 of the Application demonstrate the significant benefit of administering reduced glutathione (i.e., apart from the glutathione that naturally exists in the subject) in combination with nitrosated albumin. Examples 1-3 are a direct comparison between the claimed invention and a technique similar to the one described in *Hallström* (i.e., no administered glutathione). The fact that administering glutathione provides a significant benefit over the *Hallström* technique is a surprising and unexpected result that would not be obvious from the combined teachings of *Schlag* and *Hallström*.

In addition, Applicants also note that *Schlag* specifically mentions that the use of a small protein such as glutathione is not preferred. (*Schlag*, col. 2, line 62). A person of ordinary skill would not expect a non-preferred and specifically discouraged embodiment (i.e., administration of glutathione either alone or with another protein) would provide the kind of positive and synergistic effects that are described in Examples 1-3 of the present Application. As such, Applicant respectfully submits that a person of ordinary skill would not have chosen the combination of S-nitroso albumin and reduced glutathione from the many possibilities that are listed in *Schlag*. In sum, Applicant respectfully submits that the only motivation for combining S-nitroso albumin and reduced glutathione based on the disclosure of *Schlag*, either with or without the combination of *Hallström*, comes from an improper use of hindsight based on the claims and written description of the present Application.

For at least the reasons listed above, Applicant respectfully submits that the combination of *Schlag* and *Hallström* fails to render the present claims obvious because the claimed combination fails to teach or suggest each and every element of the claims and the claimed combination provides surprising and unexpected results that are neither taught nor suggested in the cited references. Likewise, Applicant respectfully submits that a person of ordinary skill would not choose the claimed combination of S-nitroso albumin and reduced glutathione from the many possibilities that are listed in *Schlag*, either with or without the teachings of *Hallström*. In addition, Applicant respectfully submits that claims 2, 7, and 14 include additional elements that further distinguish over the art of record. Reconsideration and allowance of claim 1 and the claims that depend thereon is respectfully requested.

**E. CONCLUSION**

In view of the foregoing, Applicant respectfully submits that the other rejections to the claims are now moot and do not, therefore, need to be addressed individually at this time. It will be appreciated, however, that this should not be construed as Applicant acquiescing to any of the purported teachings or assertions made in the last action regarding the cited art or the pending application, including any official notice. Instead, Applicant reserves the right to challenge any of the purported teachings or assertions made in the last action at any appropriate time in the future, should the need arise. Furthermore, to the extent that the Examiner has relied on any Official Notice, explicitly or implicitly, Applicant specifically requests that the Examiner provide references supporting the teachings officially noticed, as well as provide the required motivation or suggestion to combine references with the other art of record.

For at least the foregoing reasons, Applicant respectfully submits that the pending claims are neither anticipated by nor made obvious by the art of record. In the event that the Examiner finds any remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, the Examiner is requested to contact the undersigned attorney.

Dated this 13th day of January 2011.

Respectfully submitted,

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